AF 1625

CASE 4-30028/A/PCT

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Joseph J. Borovian	Joseph J. Borovian	April 16, 2001
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

PORTMANN ET AL.

Art Unit: 1625

Examiner: P. Morris

INTERNATIONAL APPLICATION NO: PCT/EP 98/03427

FILED: 8 JUNE 1998

U.S. APPLICATION NO: 09/125,329

35 USC §371 DATE: 8 SEPTEMBER 1998

FOR: CRYSTAL MODIFICATION OF 1-(2,6-DIFLUOROBENZYL)-1H-1,2,3-TRIAZOLE-4-CARBOXAMIDE AND ITS USE AS ANTIEPILEPTIC

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the decision of the Examiner dated October 13, 2000, finally rejecting Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 (Claims 27 and 29 were withdrawn by the Examiner in said Office Action and cancelled by the Appellants in the Amendment under 37 CFR 1.116 filed January 19, 2001).

REAL PARTY IN INTEREST

The real party in interest in the instant Appeal is Novartis AG, a company organized under the laws of the Swiss Confederation, of 4002 Basle, Switzerland.

RELATED APPEALS AND INTERFERENCES

There are no interferences known to Appellants or Appellants' representatives which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

STATUS OF THE CLAIMS

Claims 10-12, 15, 22-25, 27 and 29 have been cancelled and Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 stand rejected. No claims have been allowed. The claims on appeal are Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 as set out in the attached Appendix.

STATUS OF THE AMENDMENTS

The Amendment under 37 CFR 1.116 filed January 19, 2001 was entered. In this connection, since Section 3 of the Advisory Action indicates that the Amendment to the Final Rejection will be entered upon the filing of an Appeal, it is clear that the checking off of Boxes 1a) and 1d) of the Advisory Action does not make sense and that the inclusion of the claims cancelled by said Amendment among the list of "rejected" claims is due to an advertence.

SUMMARY OF THE INVENTION

The invention defined by the claims under appeal relates to two different crystalline forms of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, which forms are identical, with the exception that one of the forms has defects in the crystal lattice characterized by line spacings which are smaller compared to the other form (see Claims 1-9, 13, 14, 16-21, 30 and 31 in the Appendix), and to pharmaceutical compositions containing said crystalline forms (see Claims 26 and 28 in the Appendix).

ISSUES ON APPEAL

The issues of this Appeal are as follows:

1. Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 stand rejected under 35 USC 102(a), (b), (e) and/or (f) as being anticipated by Meier I (European Patent 199,262) and Meier II (USP 4,789,680), the latter of which is the U.S. equivalent of the European patent.

2. Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 stand rejected under 35 USC 103 as being unpatentable over Meier I and II (as identified above) in view of Munzel I (Progress in Drug Research, 10:227-230 (1966)) and Munzel II (Progress in Drug Research, 14:309-321 (1970)).

3. Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 stand rejected under the second paragraph of 35 USC 112 as being "indefinite" in two respects.

4. Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 stand rejected under the judicially created doctrine of "obviousness-type double patenting" as being unpatentable over Claims 1-10, 14, and 20 of USP 4,789,680 (referred to above and hereinafter as Meier II) in view of Munzel I and II (as identified above).

5. Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 stand rejected under the judicially created doctrine of "obviousness-type double patenting" as being unpatentable over the claims of co-pending U.S. Application No. 09/599,699 in view of Munzel I and II (as identified above).

GROUPING OF THE CLAIMS

In resolving the issues of this Appeal, all of the claims, i.e., Claims 1-9, 13, 14, 16-21, 30 and 31, which are directed to the two crystalline forms, per se, and Claims 26 and 28, which are directed to pharmaceutical compositions containing said crystalline forms, stand or fall together.

ARGUMENTS

1. Since neither the teachings of Meier I nor the teachings of Meir II anticipate any of the appealed claims, the 35 USC 102(a), (b), (e) and/or (f) rejection should be overturned.

As indicated above, Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 have been rejected under 35 USC 102(a), (b), (e) and/or (f) as being anticipated by Meier I (European Patent 199,262) and Meier II (USP 4,789,680), the latter of which is the U.S. equivalent of the European patent. More particularly, it is the Examiner's contention that since Example 4 of Meier I and Example 35 of Meier II disclose a crystalline form of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide from ethanol, said examples anticipate all of the claims presently on appeal. In this connection, the Examiner relies on certain case law in an effort to support her position. Appellants respectfully disagree with the Examiner's conclusion and believe that neither the teachings of Meier I nor the teachings of Meier II anticipate any of the appealed claims.

Although Appellants agree with the propositions set forth in the case law relied upon by the Examiner, it is Appellants' belief that they are inapplicable to the present fact situation. Quite simply, the Meier I and Meier II references are devoid of any mention that the compound 1-(2,6-difluorobenzyl-1H-1,2,3-triazole-4-carboxamide can exist in different crystalline forms, let alone the specific crystalline forms to which the appealed claims are limited. The mere disclosure of a single compound does in no way suggest the existence of a group of polymorphic forms, as alleged by the Examiner. There is clearly no class or genus of compounds suggested by the Meier references which could be held to consist of compounds that, in view of the case law relied upon by the Examiner, could anticipate any of the crystalline forms of the appealed claims. Moreover, the crystalline forms of the appealed claims are characterized by characteristic lines at interplanar spacings as determined by means of an X-ray powder pattern. Accordingly, neither the teachings of Meier I nor the teachings of Meier II anticipate any of the crystalline forms of the appealed claims, since each and every element of the invention of the appealed claims is not disclosed by either the Meier I or Meier II references. (See, in this connection, Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 91 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987) ("every element of the claimed invention must be identically shown in a single reference").

For essentially the reasons discussed above, Appellants do not believe that the pharmaceutical compositions of appealed Claims 26 and 28 are anticipated by the teachings of Meier I or Meier II. Since the crystalline forms of the claimed pharmaceutical compositions are not anticipated, the claimed pharmaceutical compositions are not anticipated.

2. Since the combined teachings of the Meier and Munzel references do not render any of the appealed claims *prima facie* obvious, the 35 USC 103 rejection should be overturned.

As indicated above, Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 have been rejected under 35 USC 103 as being unpatentable over Meier I and Meier II (as identified above) in view of Munzel I and Munzel II (as identified above). More particularly, it is the Examiner's contention that since the Meier references disclose a crystalline form of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, save for the lines with interplanar spacings of the X-ray powder pattern of said form or any other characterizing parameters, and since the Munzel references teach that compounds can exist in different polymorphic forms which retain the activity of the compounds, the crystalline forms of the appealed claims would have been *prima facie* obvious to one skilled in the art from the combined teachings of the references. Appellants respectfully disagree and believe that the combined teachings of the Meier and Munzel references do not prejudice the patentability of any of the appealed claims from a 35 USC 103 standpoint.

Appellants readily acknowledge that Example 4 of Meier I and Example 35 of Meier II have the same chemical formula as the compound of appealed Claims 1 and 7, the scopes of which are directed to two different crystalline forms of said compound. However, as the Court stated in re Cofer, 148 USPQ 57: "a new crystalline form of a compound would not be obvious absent evidence that the prior art suggests the particular structure or form of the compound and a suitable method of obtaining that form of structure". Accordingly, the salient question to be asked is whether the Meier references relied upon by the Examiner satisfy the strictures set forth in the Cofer decision supra? It is quite clear that one can only answer this question in the negative. Thus, no more than a cursory review of the Meier references reveals the fact that they are silent with regard to even a hint of a recognition that the specific compound alluded to above can exist in different crystalline forms, let alone contains any suggestion that different crystalline forms could or should be made or how any of the crystalline forms can be obtained. This, Appellants

respectfully submit, is a critical deficiency of the Meier references. Without an obvious method of making Appellants' claimed crystalline forms, they cannot be obvious under 35 USC 103 (see, in this connection, In re Hoeksema, 58 USPQ 596). Appellants respectfully submit that different crystalline forms of a compound are not inherent or structurally obvious unless there is a clear teaching or some chemical theory which supports this conclusion (see, in this connection, In re Grose, 201 USPQ 57). In the instant case, there is no clear teaching or chemical theory which would render either of Appellants' claimed crystalline forms and the method of obtaining them prima facie obvious.

In an effort to dispel any lingering doubts regarding the deficiency of the teachings of the Meier references to the crystalline forms of the appealed claims, the attention of the Board is respectfully invited to two documents which are of record, hereinafter referred to as Document 1 and Document 2. Document 1, entitled "Kenndaten für Praeparat CGP 33101", is dated January 20, 1987 and is signed by René Meier, who is the sole patentee of the two Meier references relied upon by the Examiner. Section 4 of Document 1, entitled "Polymorphism", reads as follows: "Have observations been made, which lead one to suppose that different crystal modifications exist (e.g., clear visual differences in crystal aspect when crystallized from different solvents, different melting points; variable IR spectra for presumably same degree of purity)". From this, it is clear that René Meier himself, a man skilled in the art, was unaware that CGP 33101 (a.k.a., Example 4 of Meier I and Example 35 of Meier II) existed in different polymorphic forms. Document 2, entitled "Biopharmaceutical Data Collection - CGP 33101", is dated May 27, 1987. In the table below the section heading "Polymorphism and Hydrates" on Page 1, there is disclosed characterizing data for a single neutral compound in crystalline form and a reference to Document 1 (see the last column of the table). From this, it is clear that Document 2 is devoid of any teaching that point to the existence of different crystalline forms for CGP 33101. In brief, not only was René Meier unaware that CGP 33101 existed in different polymorphic forms at the time the earliest in the family of U.S. cases which eventually matured into USP 4,789,680 was filed (i.e., December 16, 1983), but Documents 1 and 2 clearly establish that more than three years later René Meier, a man skilled in the art, in spite of his knowledge that any compound may show polymorphism, not only doubted that CGP 33101 existed in different polymorphic forms, but was not motivated to investigate the "polymorphism" aspect of CGP 33101.

As to the Munzel I and Munzel II references, neither of these references cures the deficiency of the Meier references relied upon by the Examiner. Admittedly, the Munzel

references teach that compounds can exist in different polymorphic forms. However, this represents no more than what is already known in the prior art and, as indicated above, this knowledge failed to motivate René Meier to investigate the "polymorphism" aspect of CGP 33101. Accordingly, the combined teachings of the Munzel and Meier references do not suggest the existence of Appellants' claimed crystalline forms and certainly nothing which would suggest how they can be obtained. At best, the combined teachings of the Munzel and Meier references represent an "invitation to experiment" which is insufficient under 35 USC 103. To wit, although the syntheses described in Example 4 of Meier I and Example 35 of Meier II results in the obtainment of 1-(2-6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide in solid form, the description is devoid of any mention of any crystal modification or mixture thereof. In fact, upon reproducing the examples, one skilled in the art would still be unaware of the existence of crystalline forms or how they can be obtained, since the crystallization conditions (e.g., concentration, quality of the solvent, quality of the crude product, temperatures, type of crystallization such as seeding, change in temperatures, etc.) are absent. In addition, from the melting point set forth in said examples, no definitive conclusion can be drawn that any crystalline form was present at room temperature, since, by heating, a transformation can take place. Therefore, the mere indication of the temperature does not allow for any characterization of the solid product obtained. Still further, it is not even possible to presume which crystalline form has actually melted.

In conclusion, there must be a suggestion or teaching in the prior art that the "new" crystalline forms discovered by the Appellants could or should be made, whether by manipulation of the prior art process being relied upon or by some other process. Clearly, there is nothing in the combined teachings of the Meier and Munzel references or any other prior art which would suggest or teach that crystalline forms of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide exist and that they could or should be made. Nor, more importantly, is there anything in the combined teachings of the Meier and Munzel references or any other prior art which would suggest or teach a method of making the crystalline forms of the appealed claims.

In view of the foregoing, it is clear that the crystalline forms of the appealed claims are unobvious and patentable over the combined teachings of the Meier and Munzel references.

For essentially the reasons discussed above, Appellants do not believe that the pharmaceutical compositions of appealed Claims 26 and 28 are rendered *prima facie* obvious by the combined teachings of the Meier and Munzel references. Appellants submit that it is not

obvious to prepare a pharmaceutical composition when the motivation to do so is totally absent from the prior art, as is the case in the instant rejection. It is clear that there is nothing in the combined teachings of the Meier and Munzel references which would provide one skilled in the art with the motivation to prepare the pharmaceutical compositions of appealed Claims 26 and 28. Since the crystalline forms of the claimed pharmaceutical compositions are novel and unobvious, the claimed pharmaceutical compositions are novel and unobvious.

3. Since the presence of the expression "essentially pure form" and the phrase "but has defects in the crystal lattice" do not render certain of the appealed claims "indefinite", the rejection under the second paragraph of 35 USC 112 should be overturned.

First of all, Appellants do not agree that the expression "essentially pure form" in certain of the appealed claims is meaningless. As can be seen from the fourth complete paragraph on Page 10 of the instant specification, the expression "essentially pure form" means a purity of >95%, in particular, >98%, primarily >99%. Thus, one skilled in the field of "polymorphic forms" would clearly understand that the expression "essentially pure form" is intended to mean "essentially free of any other polymorphic forms".

Secondly, Appellants do not agree that the phrase "but has defects in the crystal lattice" renders certain of the appealed claims which are directed to crystal modification A' indefinite and their scopes unascertainable. It is clear from the third paragraph on Page 2 of the instant specification that the phrase refers to "smaller line spacings" as detected by X-ray analysis, when compared to crystal modification A.

As to the Examiner's comment that Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 are substantial duplicates, Appellants respectfully disagree. Claim 1 is intended to claim a specific crystalline form of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, viz., crystal modification A, and characterizes said crystalline form with sufficient particularity. As to the other crystalline form, viz., crystal modification A', it is identical to crystal modification A, save for smaller line spacings as detected by X-ray analysis (see the discussion in the preceding paragraph). In any event, since it is Appellants' belief that the scope of Claim 1 embraces a crystalline form, with and without defects in its crystal lattice, Claim 7 as well as other claims which depend or ultimately depend on Claim 1, are properly dependent.

4. Since the combined teachings of Meier II and the Munzel references do not render any of the appealed claims *prima facie* obvious, the "obviousness-type double patenting" rejection over certain of the claims in Meier II should be overturned.

As indicated above, Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 have been rejected under the judicially created doctrine of "obviousness-type double patenting" as being unpatentable over Claims 1-10, 14 and 20 of USP 4,789,680 (referred to above and hereinafter as Meier II) in view of Munzel I and II (as identified above). More particularly, it is the Examiner's contention that since Meier II discloses a crystalline form of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide and since the Munzel references teach that compounds can exist in different polymorphic forms, the appealed claims are not patentably distinct over certain of the claims in Meier II. Appellants respectfully disagree with the Examiner's contention and her conclusion of "obviousness".

The deficiencies of the combined teachings of Meier II and the Munzel references relative to the appealed claims has been indicated above regarding the 35 USC 103 rejection and, accordingly, all of the foregoing arguments apply.

Quite simply, there is nothing in the combined teachings of the Meier II and the Munzel references which would suggest or teach that crystalline forms of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide exist and that they could or should be made. Nor, more importantly, is there anything in the combined teachings of the Meier II and Munzel references which would suggest or teach a method of making Appellants' claimed crystalline forms.

In view of the foregoing, it is clear that Appellants' claimed crystalline forms are unobvious and patentable over the combined teachings of the Meier II and Munzel references.

For essentially the reasons discussed above, Appellants do not believe that the pharmaceutical compositions of appealed Claims 26 and 28 are rendered *prima facie* obvious by the combined teachings of the Meier II and Munzel references. Since the crystalline forms of the claimed pharmaceutical compositions are novel and unobvious, the claimed pharmaceutical compositions are novel and unobvious.

In short, the appealed claims are patentably distinct over certain of the claims in Meier II.

5. Since the combined teachings of co-pending U.S. Application No. 09/599,699 and the Munzel references do not render any of the appealed claims *prima facie* obvious, the "obviousness-type double patenting" rejection over certain of the claims in said co-pending application should be overturned.

As indicated above, Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31 have been rejected under the judicially created doctrine of "obviousness-type double patenting" as being unpatentable over the claims of co-pending U.S. Application No. 09/599,699 in view of Munzel I and II (as identified above). More particularly, it is the Examiner's contention that since co-pending U.S. Application No. 09/599,699 discloses a crystalline form of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, viz., crystal modification B, and since the Munzel references teach that compounds can exist in different polymorphic forms, the appealed claims are not patentably distinct over the claims in co-pending U.S. Application No. 09/599,699. Appellants respectfully disagree with the Examiner's contention and her conclusion of "obviousness".

Admittedly, co-pending U.S. Application No. 09/599,699 claims crystal modification B of the compound 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, as noted by the Examiner and, in fact, crystal modification C of said compound and additionally mentions the existence of crystal modifications A and A', i.e., the two crystalline forms to which the appealed claims are directed. However, since co-pending U.S. Application No. 09/599,699 is silent with regard to any teaching as to how the specific crystalline forms of the appealed claims can be prepared and since the Munzel references do not cure this defect, it is clear that Appellants' crystalline forms are unobvious and patentable over the combined teachings of co-pending U.S. Application No. 09/599,699 and the Munzel references.

For essentially the reasons discussed above, Appellants do not believe that the pharmaceutical compositions of appealed Claims 26 and 28 are rendered *prima facie* obvious by the combined teachings of co-pending U.S. Application No. 09/599,699 and the Munzel references. Since the crystalline forms of the claimed pharmaceutical compositions are novel and unobvious, the claimed pharmaceutical compositions are novel and unobvious.

In short, the appealed claims are patentably distinct over the claims in co-pending U.S. Application No. 09/599,699.

In any event, if the Board affirms this "obviousness-type double patenting" rejection and if either the present application or the co-pending application is allowed, it is Appellants' intent to file a Terminal Disclaimer in the other application.

CONCLUSION

For the foregoing reasons, none of the claims on appeal, i.e., Claims 1-9, 13, 14, 16-21, 26, 28, 30 and 31, : 1) is anticipated by the teachings of Meier I or Meier II; 2) is rendered *prima facie* obvious over the combined teachings of the Meier and Munzel references; 3) contains an expression and/or phrase which renders it indefinite under the second paragraph of 35 USC 112; 4) is patentably indistinct over certain of the claims in Meier II; and 5) is patentably indistinct over the claims in co-pending U.S. Application No. 09/599,699. Reversal of all of the rejections on appeal is, therefore, respectfully requested.

In accordance with 37 CFR 1.192(a), two additional copies of this Appeal Brief are submitted herewith.

Please charge the $310.00 fee required by 37 CFR 1.17(c) for filing an Appeal Brief to Deposit Account No. 19-0134 in the name of Novartis Corporation. Two additional copies of this page are appended.

Respectfully submitted,

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Attachment: Two additional copies of Appeal Brief
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